

IMPAIRED IMMUNITY: A VIEW OF CURRENT STIGMATA AND DISEASE EVALUATION*

STEPHEN D. LITWIN, M.D.

Department of Medicine
Cornell Medical College
New York, New York

IMPAIRED immunity is conceptually best viewed as one pole of a continuum of disturbed immune function rather than as a discrete event.

Certain considerations should guide analysis of immune impairment in an individual. To begin with, immune deficiency disease is a relative concept and the stigmata encountered—infection, malignancy, autoimmunity—are all found in healthy persons and other disorders. Only in the face of repeated, severe, and inappropriate appearance of problems can it be concluded that there is a breach in host defenses. As a relative concept, we should not demand that it be all or none but expect gradations in the disease picture. The first human immune deficiency was labeled agammaglobulinemia (no immunoglobulins) only to be gradually replaced with the more accurate term (low) hypogammaglobulinemia. Many evaluations of immune function are performed *in vitro* and are not identical to the *in vivo* immune lesions. Tests which appear more physiologic, such as measurement of specific antibody titers following immunization, are highly restricted and do not reflect the full spectrum of the immune response. Despite these pitfalls it is clear that the parallel between clinical immune deficiency states and the tests we use to evaluate them is operationally satisfactory.

EVALUATION OF IMMUNE IMPAIRMENT IN HOST DEFENSE SYSTEMS

Host defenses operate on multiple levels and interact across these levels. Their individual existence is best appreciated in their absence. Selected defense systems and disease examples of defects are seen in

*Presented as part of a course, *Review of Procedures Used in the Practice of Allergy*, presented by the Columbia University College of Physicians and Surgeons and the American Academy of Allergy at the New York Academy of Medicine November 5-7, 1980.

This work was supported in part by grant CA 24438-10 from the National Cancer Institute, Bethesda, Md.

TABLE I. HOST DEFENSE SYSTEMS IN WHICH IMPAIRMENT IS KNOWN

<i>Type of immunity</i>	<i>Example of a defect</i>
Antibody-mediated	Infantile sex-linked immune deficiency
Cell-mediated	Nucleoside phosphatase deficiency
Complement, classic and alternate pathway	C ₃ deficiency
Phagocytosis and intra-cellular killing	Chronic granulomatous disease
Splenic	Sickle cell anemia
Intactness and function of skin? mucous membranes? cilia	Burns, immotile cilia syndrome
Local, including gut and bronchial associated lymphoid tissue, antibacterial action of various agents	IgA deficiency
Immune regulation	Rare cases of immune deficiency, systemic lupus erythematosus

Table I: other immune defenses undoubtedly exist but remain undefined because of lack of a simple disease model. Neither classic antibody-mediated immunity nor cell-mediated immunity are single events but rather a complex sequence of reactions in which we monitor only a single point. Tests of early or midlevel events, such as surface Ig on B cells or the mitogenic response of T lymphocytes have the advantage of being better defined and better focused than such tests of endpoint functions as delayed cutaneous hypersensitivity or specific polio antibody production because they are perturbed only by the steps preceding them. Endpoint testing tends to be more inclusive and thus is more effective as a screen. (Lockshin has discussed aspects of this problem for cell-mediated immunity.)¹ Too much emphasis should not be placed on the linearity of B or T cell pathways because evidence is increasing of regulatory feedback loops. Both antibody-mediated and cell-mediated immunity can be tested with either specific antigens versus challenge to develop a polyclonal response, e.g., measurement of polio antibody versus serum, immunoglobulins or blastogenic response to old tuberculin versus phytohemagglutinin. The immune response may also be classified as to whether it is to an antigen previously encountered (see Table III) or an entirely novel one, but in actuality this is a difficult distinction to make with confidence.

Increasing sophistication has rapidly expanded the capability of auditing the deranged or deficient complement pathway. C1r, C4, and C2 defects are associated with vasculitis and lupuslike diseases: C3 or C3b inhibitor

TABLE II. EXAMPLES OF POSSIBLE SYNERGY BETWEEN IMPAIRED HOST DEFENSE SYSTEMS

<i>Example of an individual with</i>	<i>Defects in</i>
1. Multiple myeloma receiving cytotoxic agents	Antibody-mediated and cell-mediated immunity and excess suppressor cell activity
2. Alcoholism and variable immunodeficiency disease	Polymorphonuclear leukocyte chemotaxis, antibody-mediated and ? cell-mediated immunity
3. IgA deficiency and hereditary C ₂ deficiency	C function and local immunity
4. Wiskott-Aldrich syndrome and splenectomy	Splenic immunity and antibody-mediated immunity (partial)

deficiencies with repeated pyogenic bacterial infections: C5, 6, 7, 8 defects with infection with *Neisseria*. The distinctions between classic and alternate pathways are evident in this classification although the exact defense role of the latter is still unresolved.

Participation of the spleen in immune defenses has not been fully appreciated in the past.² Recent data confirm that risk of infection is considerably higher even in those who have had their spleens removed for trauma, although the underlying disease does modify the degree of risk. Estimates of a six to ninefold increase in the incidence of bacterial infection, and 30 to 200-fold increase in fatal infections have been published.

Local host defense factors are poorly defined. For example, it is not clear whether all of the various protease inhibitors in serum and secretory fluids constitute a critical defense link to delimit inflammation, a possibility raised by alpha 1-antitrypsin associated pulmonary emphysema.

The regulation of antibody-mediated and cell-mediated immunity is far more intricate, indirect, rich in feedback loops and cell-to-cell interactions than previously appreciated. Abnormal positive or negative regulation has been documented in immunodeficiencies,³ graft-vs.-host disease,⁴ infectious mononucleosis,⁵ multiple myeloma, and systemic lupus erythematosus, among others. The direct issue of whether the aberrant regulation is secondary is in most cases not resolved. It is predictable that *primary* inherited or acquired defects in these regulatory mechanisms will be encountered at some point.

For the sake of the clearest possible analysis of immune pathophysiology, we classify the host-defense systems involved and systematize de-

TABLE III. EVALUATION OF THE IMMUNE RESPONSE

	Basic	Response to previous antigenic exposure	Response to new antigen	Specialized	Limited in use
Antibody-mediated immunity	Serum electrophoresis and quantitative IgG, IgA, IgM, IgE	Isohemagglutinins (usually IgM) Antistreptococcal antibody or Schick test (usually IgG). Polio, tetanus, rubella, typhoid antibody	Polio, tetanus, typhoid antibody after immunization: Phage X174	B Cell enumeration SIg+ cells CIg+ cells Ia+ cells c receptor cells Proliferative or Ig response to pokeweed mitogen and other B cell mitogens Autoantibodies	Specific IgE (RAST) K/ λ ratio IgG subclasses IgD Secretory Ig Metabolism Ig's Biopsy lymphoid tissue
Cell-mediated immunity	Absolute lymphocyte ct. (50-80% usually T cells) Lymphocyte blastogenic response to T Cell mitogens (PHA, CON-A, Mixed leucocyte reaction Delayed cutaneous hypersensitivity with 5 or 6 antigens CH ₅₀ total hemolytic complement C ₃ & C ₄ assay	Lymphocyte blastogenic response to antigens	DNCB	T cell enumeration: SRBC rosettes, Ty, Tu, and subsets Assay T cell suppressor/helper activity Thymus on radiograph Cytotoxicity against target cells	Rebuck skin window (25% macrophages at 24 hrs) Lymphokine production incl. MIF Thymic hormones Allograft rejection
Complement				C' esterase inhibitor	Radioimmunoassay of specific components Opsonization capacity

C = complement, SIg and CIg = surface and cytoplasmic Ig resp., SRBC = rosettes formed with sheep red blood cells.

scription of the clinical damage expected. For the organism, the *totality* of defense mechanisms is crucial, and we should anticipate synergy between immune defects. Because so much modern therapy and modern disease compromises immune function (radiation, cytotoxic drugs, immunosuppressive regimens for tissue transplantation, uremia, burns, prolonged malignancies, splenic infarction in sickle cell anemia) the number of such potentially synergistic situations expands geometrically. Table II lists several examples, some of which are not rare. It should be emphasized that the pattern of disease is not only more severe when two types of defects are encountered but may be *qualitatively* novel and pose new problems.

An outline of basic and specialized tests for immune function is found in Table III. In antibody-mediated immunity those responses which are predominantly IgG should be distinguished from those which are IgM. The response to earlier antigenic exposure compared to recent immunization should demarcate lesions involving memory cells from those involving cells that proceed immediately to terminal differentiation. A suggestion of a rare case of this sort is found in a report of a transcobalamin II (B₁₂ transport protein) deficient individual who responded to Vitamin B₁₂ with specific antibody to "remembered" antigens without further immunization.⁶ The enumeration of T and B lymphocytes was a first step in delineating subsets of lymphocytes that subserve individual immune functions. In addition to T_H1 and T_H2 and the T_H2+ and T_H2- subsets, new subpopulations are already being tested, some of the resolution flowing from the monoclonal antibody technique. Finally, a last point is that B and T cells are not defined solely by single antigens but also by combinations of antigenic markers. An example is the interest in the role of Ia + T cells found in the blood during certain immune abnormalities and during immune response.⁷ Special tests, including those in Table III, are too numerous to be detailed. Their proper application requires skill in clinical diagnosis and is based in part on results of previous laboratory data.

GENETIC FACTORS IN PRIMARY IMMUNODEFICIENCY

In evaluating immune impairment, there are three major sources of information—the laboratory studies already discussed, clinical signs, and family history. The last should not be underestimated. The majority of immunodeficiency diseases show either familial clustering of disease or a

TABLE IV. HEREDITY IN PRIMARY IMMUNODEFICIENCIES

	<i>Monogenic*</i> <i>trait</i>	<i>Familial</i>	<i>Little or no</i> <i>genetic</i> <i>component</i>
<i>Stem cell defects</i>			
Severe combined immunodeficiency			
ADA negative	AR		
ADA positive	X		
ADA positive (swiss type)	AR		
ADA positive			Sporadic
<i>B cell defects</i>			
Infantile sex-linked immunodeficiency	X		
Congenital hypogammaglobulinemia	AR		Or sporadic
Variable immunodeficiency		Familial	Or sporadic
Selective IgA deficiency		Familial	Or sporadic
Selective IgM deficiency?			
IgG subclass deficiency?			
Hyper IgM	Many X		Some sporadic
Immunodeficiency with normal or high Ig	X		Or sporadic
Immunodeficiency with thymoma			Sporadic
<i>T cell defects</i>			
Nezelof syndrome		Familial	Or sporadic
DiGeorge syndrome†			
Nucleoside phosphorylase defic.	AR		
Chronic mucocutaneous candidiasis with endocrinopathy	AR		Or Sporadic
<i>Complex Immunodeficiency</i>			
Wiskott-Aldrich syndrome	X		
Ataxia telangiectasia	AR		
Hyper IgE syndrome?			
Cartilage hair hypoplasia with dwarfism	AR		

*AR is a disorder inherited as an autosomal recessive trait; X as an x-linked trait.

ADA = adenosine deaminase.

†Too little information to comment on mode of inheritance.

well-defined monogenic pattern of inheritance. Table IV lists many of the known primary immunodeficiency diseases by cellular site of the defect. Overlapping pathology is common, e.g., variable immunodeficiency disease and selective IgA deficiency have T cell defects in some cases. Among the complex immunodeficiency diseases, ataxia telangiectasia might better be regarded as a T cell problem, Wiskott-Aldrich disease as a B cell problem. Only two of 21 primary immunodeficiency diseases fail to show familial aggregation: in four of the disorders the information is very limited. Many of the major immunodeficiency states, including variable immunodeficiency disease, severe combined immunodeficiency disease,

and congenital hypogammaglobulinemia show genetic heterogeneity; some cases are sporadic and others familial without distinguishing features. Selective IgA deficiency is the most common immune deficiency encountered, and is as frequent as one per 500 births (there can be up to half a million cases in the United States, most of whom are probably in good health). There are families in which this disease occurs repeatedly and in which the pattern can be interpreted as that of a recessive or dominant trait, but analysis of a large number of kindreds is disappointing in that no convincing pattern of genetic transmission is present. The genetic factors in variable immunodeficiency disease are also perplexing. Most cases lack a family history and the limited number of pedigrees that show multiple involvement usually disclose a "cluster" of immune-related problems rather than panhypogammaglobulinemia. This cluster may include selective IgA deficiency, autoimmune hemolytic anemia, lymphoma, systemic lupus erythematosus, thrombocytopenia, and others. One clue to the interweaving of disease entities in these families may be found in the description of the X-linked lymphoproliferative syndrome by Purtilo.⁸ One family with this inherited disorder, in whom presumably all affected members had the same mutant gene, showed three different patterns of disease. Some cases died of Epstein-Barr virus infection, almost always a self-contained illness under ordinary circumstances. Hypoplastic cases with aplastic anemia and hypogammaglobulinemia contrast to the hyperplastic group which presented with Burkitt lymphoma (another unusual entity in the United States), multiple myeloma, and lymphomas of other types. The alternate pathways of disease evoked by unknown factors in which all affected members inherited the same gene suggests that the spectrum of immune disease is broad, and can show very diverse manifestations.

STIGMATA OF IMMUNE IMPAIRMENT

Prior to antibiotics, the overwhelming consequences of infection submerged all other sequelae of immune impairment. As we have become more effective in treating infection we have been rewarded by the dubious privilege of viewing other complications of faltering immune mechanisms, and are still being astounded and fascinated by the unexpected relationships that are surfacing. Some of these are listed in Table V.

Infection. The nature and extent of immune impairment on one hand and the vulnerability to exploitation by opportunistic pathogens on the

TABLE V. STIGMATA OF IMPAIRED IMMUNITY

- | |
|---|
| 1) Infection |
| 2) Malignancy |
| 3) Autoimmunity |
| 4) Atopy |
| 5) Vulnerability to invasion by attenuated viruses, immunocompetent cells |

other are biologically interlocked. The simple statement that the former determines the latter is widely appreciated. The obverse is also true, i.e., the invasive microorganism, in an indirect sense, describes the immune lesion. These relationships are illustrated in different ways in Table VI and VII. Table VI is a useful classification of the most prevalent pathogens found in the broad types of immune deficits.⁹ Its application varies. Overlap restricts interpretation in high-grade pyogenic infections which may arise as a result of problems in antibody-mediated immunity, classic C pathway defects, the Wiskott-Aldrich syndrome, and the immotile cilia syndrome among others. On the other hand, *Listeria monocytogenes* infection is relatively restricted to defects in cell-mediated immunity. Repeated infection reinforces the interpretation of a disease pattern. Table VII utilizes the same basic relationship and lists pathogens that characterize specific disease entities. The generalization that antibody-mediated immunity is associated with bacterial and cell-mediated immunity with viral and fungal illness overlooks much useful information. It will be important in the future to focus and to define even further the intricacies of the immune impairment-microorganism relationship. One example of this trend is the observation that *Pneumocystis carinii* infection in children with lymphocytic leukemia receiving chemotherapy can be forestalled by prophylaxis with trimethoprim-sulfamethoxazole.¹⁰ In many diseases the boundary between immune systems is not easily demarcated and the relative contribution of each is unclear. Poliomyelitis, an enterovirus, has a complex natural history involving both antibody-mediated and cell-mediated immunity. The Medical Research Council Working Party report showed an attack rate for paralytic polio in hypogammaglobulinemic children of 1.7/1,000 patients per year while the population at large had a rate of 0.2/1000. Two of the 28 hypogammaglobulinemic children who received polio vaccine excreted virus for a prolonged period. The immune deficient children who became ill did not have problems in cell-mediated immunity.¹¹ Although the figures attest to the higher risk for enterovirus

TABLE VI. INFECTIOUS AGENTS CAUSING DISEASES THAT FREQUENTLY COMPLICATE INFLAMMATORY AND IMMUNODEFICIENCY DISORDERS

	Antibody-mediated immunity			Cell-mediated immunity (T lymphocytes & macrophages)
	Phagocytes (neutrophils)	Complement	Antibody	
Bacteria				
Gram-positive cocci	+++	++	+++	
Enterobacteriaceae	+++	+	+	
Pseudomonas aeruginosa	+++	+	+	
Haemophilus influenzae	+	+	+++	
Salmonella sp.				+++
Listeria monocytogenes				+++
Mycobacterium tuberculosis				+++
Nocardia asteroides				+++
Fungi				
Candida sp.				
Systemic	++			
Chronic mucocutaneous				+++
Aspergillus sp.	+++			
Mucor-Absidia-Rhizopus	+++			
Cryptococcus neoformans				+++
Coccidioides immitis				+++
Histoplasma capsulatum				+++
Viruses				
Herpes simplex virus 1			+	+++
Herpes simplex virus 2			++	+++
Varicella-zoster				+++
Cytomegalovirus				+++
Vaccinia				+++
Rubella				+++
Papovaviruses				++
Enteroviruses			++	+
Hepatitis			++	+
Influenza			+	+
Adenoviruses			+	+
Parasites				
Pneumocystis carinii			++	+++
Giardia lamblia			++	+
Toxoplasma gondii				+++
Strongyloides stercoralis				+++

Reproduced by permission from Grieco, M.H.: Introduction to the Abnormal Host and Complicating Infections. In: *Infections in the Abnormal Host*. Grieco, M.H., editor. New York, York., 1980, pp. 1-10.

when antibody-mediated immunity is impaired, it is important to realize that the attack rate was still so low as to be overlooked unless specifically searched for in relatively large numbers of subjects at risk.

*Malignancy.*¹² The increase in tumors in both primary and secondary immune deficiency states has prompted the hypothesis that injury to immune surveillance mechanisms, which control the expansion of neo-

TABLE VII. RECURRENT OR PERSISTENT INFECTIONS WHICH COMPLICATE SPECIFIC DISEASES OR DISEASE GROUPS.

<i>Immune deficiency</i>	<i>Infection with</i>
Wiskott-Aldrich syndrome, B cell immunodeficiencies, Ataxia telangiectasia Immotile cilia syndrome C3 deficiency	Virulent encapsulated bacteria
C3, C5, C6, C7 or C8 deficiency C6, C8 deficiency Sickle-cell disease	<i>Neisseria meningitidis</i> <i>Neisseria gonorrhoeae</i> Virulent encapsulated bact., especially <i>S.</i> <i>pneumoniae</i>
Cystic fibrosis	<i>Pseudomonas aeruginosa</i>
Chronic granulomatosis disease	<i>Staphylococcus aureus</i> and gram-negative bacilli
Hyper IgE and Job's syndrome	<i>Staphylococcus aureus</i> and gram-negative bacilli
T cell and combined immunodeficiency	<i>Listeria monocytogenes</i> , gram-negative bacilli, some viruses
Leukocyte disorder of movement and intracellular killing	<i>Staphylococcus aureus</i> and gram-negative bacilli

plastic cells, is to blame. A 10,000-fold increase in cancer risk has been projected. Critical review of current data suggests that, while the basic trend is correct, simplistic explanations of cause and effect are unwarranted until the intricacies of the relationship can be resolved.

Critical information has been retrospectively developed through a voluntary registry, and large problems of sampling and ascertainment are inherent in the design. The immune deficient states sampled differ from one another enormously in pathology, inheritance, and the immune lesion, so broad generalizations about one immunodeficient disease may be totally invalid for others and cause anxiety to immune deficient patients who might harbor little risk. An association between immune impairment and risk of tumor does not prove a relationship. Both may arise from concomitant pathophysiology. For example, in ataxia telangiectasia, in which the risk of tumor is as high as 10%, chromosomal damage and consequent abnormalities are frequent. It is known that chromosomal

aberrations are closely linked to cancer. Finally, it should also be kept in mind that many severe immunodeficiency diseases have foreshortened life spans that underestimate actual figures and deemphasize the above relationship.

The distribution of malignancy differs in the immune deficient from that of the population at large (Table VIII): a higher fraction of patients tends to have mesenchymal malignancies rather than epithelial, and lymphoreticular non-Hodgkin's lymphoma was the most frequent single entity.¹² In variable immunodeficiency disease, epithelial tumors, in contrast, comprised approximately half the cases. Malignant reticuloendothelioses were clustered in three diseases, Wiskott-Aldrich syndrome, variable immunodeficiency disease, and ataxia telangiectasia. The five cases of stomach cancer encountered appeared suspiciously high. There were sharp differences as to which tumors complicated which immunodeficiency diseases. If we draw an analogy from the relationship between immunodeficiency diseases and infectious microorganisms, different types of immune impairment encourage different malignant states, and heterogeneity of tumor defense mechanisms is marked. Finally, inspection suggests that the sharp differences observed between immune deficient states do not correlate with the underlying T, B, or stem cell nature of the defect.

Secondary immunodeficiency similarly contributes a high risk of tumor and reinforces the relationship encountered in primary immunodeficient disease. Hoover and Fraumeni¹³ analyzed more than 6,000 worldwide kidney transplants who had received immunosuppressive therapy and estimated that the risk of lymphoma was 30 to 40-fold higher than expected, of reticulum cell sarcoma 350-fold, and of skin cancer fourfold higher. In one study of patients with multiple myeloma, the actuarial risk of acute myelocytic leukemia at 50 months was 17.4%. Patients in whom malignancies were inadvertently transplanted during kidney grafts showed, in some instances, regression of the foreign tumor after cessation of immunosuppression.

Autoimmunity. Early reports that children with agammaglobulinemia had a striking incidence of a rheumatoid arthritis-like disease were disquieting because immune mechanisms were believed to underlie the disease and immune deficient persons should be spared such problems. The initial observations appear true and many, but not all, immunodeficiency problems have an untoward incidence of both autoantibodies and "autoimmune" diseases. In a review of the literature, Stewart and Gershwin¹⁴

TABLE VIII. TISSUE DISTRIBUTION AND ESTIMATED FREQUENCY OF
MALIGNANCY WITH PRIMARY IMMUNODEFICIENCY

Total No. cases	ID	Mesenchymal					Epithelial		
		Lympho- reticular*	HD	ML	OM	NS	All other		
90	AT	60	9	0	5	3	13		
71	VID	32	5	1	1	2	30		
45	Wiskott- Aldrich	34	3	3	2	2	0		
16	sndrome Isolated	6	1	0	0	1	7		
14	IgA	7	1	2	2	0	2		
12	ISID	8	1	3	0	0	0		
8	SCID	5	1	0	0	1	1		
4	Isolated IgM	1	0	0	1	1	1		
3	ID with thymoma	3	0	0	0	0	0		
1	Igs	0	1	0	0	0	0		
1	X-linked IgM	1	0	0	0	0	1		
	Episodic lymphoma & lymphocyto- toxin	0	0	0	0	0	1		
1	Thymic hypo- plasia	1	0	0	0	0	0		
1	Transient hypogg. of infancy	1	0	0	0	0	0		
267		158	22	9	11	11	54		

*This includes lymphocytic lymphoma, histiocytic lymphoma, malignant reticuloendotheliosis, "lymphoid" leukemia, et al.
HD = Hodgkin's disease, ML = myeloid leukemia, OM = other mesenchymal, NS = nervous system, AT = ataxia-telangiectasia, VID = variable immuno-
deficiency, ISID = infantile sex-limited immunodeficiency, SCID = severe combined immunodeficiency.
From Spector, B.D., Perry, G.S., and Kersey, J.H.: Genetically determined immunodeficiency diseases and malignancy. Report from the immunodeficiency-
cancer registry. *Clin. Immunol. Immunopath.* 11:12, 1978.

TABLE IX. AUTOIMMUNE PROBLEMS REPORTED ASSOCIATED WITH SELECTIVE IgA DEFICIENCY

<i>Antibodies</i>	
Anti-IgA class and subclass antibody	
Milk and animal protein antibodies	
ANA, RF, antithyroid, antismooth muscle,	
antiparietal cell, anti-BM, anti-	
collagen, etc. antibodies.	
<i>Atopic allergy</i>	
<i>Diseases</i>	
Systemic lupus erythematosus	Sjogren syndrome
Rheumatoid arthritis	Autoimmune hemolytic
Juvenile rheumatoid arthritis	anemia
Gluten enteropathy	Inflammatory enteritis
Pernicious anemia	and colitis
Chronic active hepatitis	Idiopathic thrombocytopenic purpura
Dermatomyositis	Myasthenia gravis
Idiopathic Addison disease	Vitiligo

concluded that B cell disorders accounted for most immunodeficiency problems that manifested "autoimmunity," but it should be kept in mind that this included variable immunodeficiency disease and selective IgA deficiency in which the issue of T cell impairment is not resolved. In terms of frequency of autoimmune findings, the highest incidence was in variable immunodeficiency disease, selective IgA deficiency, and C2 deficiency; the least in ataxia-telangiectasia and Wiskott-Aldrich syndrome. In Table IX are listed the complications reported in selective IgA deficiency. Among those likely to be among the most interesting is a report of a high incidence of hay fever and asthma atopic disease in IgA deficient persons.¹⁵ Cassidy noted that 4 of 100 patients with juvenile rheumatoid arthritis and 5 of 100 patients with systemic lupus are IgA deficient as compared to the general population, in which 1 of 500 are IgA deficient.¹⁶ Other evidence of autoantibodies in selective IgA deficiency includes a high incidence of milk precipitins and of both class and subclass specific anti-IgA antibodies which have been associated with anaphylactoid reactions during blood transfusion.

The reasons for the above relationship may lie in the disordered immune regulation, particularly suppressor cells which accompany many immune perturbations. Studies of infectious mononucleosis and graft-versus-host disease demonstrate that both immune hyperactivity and suppression may be present at different points in time. It can be theorized that

monitors needed to prevent recognition of autoantigens fail to operate and provide a basis for the high risk of autoimmune disease.

SUMMARY

It is difficult to focus on single issues at the same time as achieving perspective in such rapidly changing disorders as the immune deficiencies exemplify. Selected aspects of evaluation and a review of current stigmata have been stressed in this discussion. Although the complexity and heterogeneity of these problems are not fully revealed, it is already evident that they can teach us very effectively about normal immune mechanisms and enlarge our concepts of the biologic significance of immune defenses.

REFERENCES

1. Lockshin, M. D.: Skin Testing and MIF Production in the Evaluation of Immune Functions. In: *Clinical Evaluation of Immune Functions in Man*, Litwin, S., Christian, C. L., and Siskind, G. W., editors. New York, Grune and Stratton, 1976, pp. 165-76.
2. Wilson, S. A. and Johnson, W. D.: Infections Complicating Surgical or Functional Splenectomy and Gastrectomy. In: *Infections in the Abnormal Host*, Grieco, M.H., editor. New York, York, 1980, pp. 848-68.
3. Waldmann, T. A., Blaese, R. M., Broder, S., et al.: Disorders of suppressor regulatory cells in the pathogenesis of immunodeficiency and autoimmunity, *Ann. Intern. Med.* 88:226-38, 1978.
4. Reinherz, E. L., Parkman, R., Rappaport, J., et al.: Abberations of suppressor T cells in human graft-vs-host disease. *N. Engl. J. Med.* 300:1061-68, 1979.
5. Tosato, G., Macgrath, I., Koski, I., and Dooley, N.: Activation of suppressor T cells during Epstein-Barr-virus infection. *N. Engl. J. Med.* 301:1133-37, 1979.
6. Hitzig, W. H., Doberman, U., Pluss, H. J., and Vischer, D.: Hereditary transcobalamin II deficiency: Clinical findings in a new family. *J. Ped.* 85:622-28, 1974.
7. Yu, D. J. Y., Winchester, R. J., Gibofsky, A., et al.: Peripheral blood Ia-positive T cells. *J. Exp. Med.* 151:91-100, 1980.
8. Purtilo, D.: Pathogenesis of phenotypes of an X-linked recessive lymphoproliferative syndrome. *Lancet* 2:883-85, 1976.
9. Grieco, M. H.: Introduction to the Abnormal Host and Complicating Infections. In: *Infections in the Abnormal Host*, Grieco, M. H., editor. New York, Yorke, 1980, pp. 1-10.
10. Rubin, R. H. and Swartz, M. N.: Drug therapy: Trimethoprim sulfamethoxazole. *New Engl. J. Med.* 303:426-31, 1980.
11. Medical Research Council: The assessment of the British vaccine against poliomyelitis. *Br. Med. J.* 1:1271, 1957.
12. Spector, B. D., Perry, G. S., III, and Kersey, J.H.: Genetically determined immunodeficiency diseases and malignancy: Report from the immunodeficiency-cancer registry. *Clin. Immunol. Immunopath.* 11:12-29, 1978.
13. Hoover, R. and Fraumeni, J. F.: Risk of cancer in renal-transplant recipients. *Lancet* 2:55-57, 1973.
14. Stewart, S. R. and Gershwin, M. E.: The association and relationships of congenital immune deficiency states and autoimmune disease, *Semin. Arthritis Rheum.* 9:98-123, 1979.
15. Buckely, R. H.: Immunologic Deficiency and Allergic Disease. In: *Allergy, Principles and Practice*, Middleton, E., Jr., Reed, C. E., and Ellis, E. F., editors. St. Louis, Mosby, 1978, pp. 200-16.
16. Cassidy, J. T., Burt, A., Petty, R., et al.: Selective IgA deficiency in connective tissue disease. *N. Engl. J. Med.* 280:275, 1969.